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William D Gerull

Varun Puri

Benjamin D Kozower

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The epidemiology and biology of pulmonary metastases

William D. Gerull, Varun Puri, Benjamin D. Kozower

Division of Cardiothoracic Surgery, Department of Surgery, Washington University, St. Louis, MO, USA

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Correspondence to: Benjamin D. Kozower, MD, MPH. 660 S Euclid Ave, Campus Box 8234, St. Louis, MO, 63110, USA. Email: kozowerb@wustl.edu.

Abstract: Our goal in this chapter is to explore the complex processes of metastasis and why there is a predisposition for this to occur in the lung. In addition, we aim to describe the incidence of pulmonary metastases in various contexts and based on the origin of the primary tumor. There are unique characteristics of the pulmonary system that make metastases more likely to occur in the lung than anywhere else in the body. Some of these characteristics include receiving the entire cardiac output every minute, having the densest capillary bed in the body, and being the first reservoir of most lymphatic drainage entering the venous system. There are multiple postulated routes of metastasis to the pulmonary system including hematogenous and lymphatic routes with early or late dissemination. The vascularization of pulmonary metastases is variable and complex, often recruiting supply from bronchial and pulmonary origin. There are also many biochemical factors in the tumor microenvironment that play a key role in the development of lung metastases including vascular endothelial growth factor (VEGF), interleukin-8 (IL-8), very late antigen 4 (VLA-4) and intercellular adhesion molecule 1 (ICAM-1). Studies vary widely in reported rates of pulmonary metastases due to differences in clinical study design, however, it is commonly accepted that up to half of autopsies performed on patients who died of malignancy have pulmonary metastases. In a surgical series describing the incidence of primary cancer types with resected pulmonary metastases the most common sites were thyroid, colon, breast, genitourinary tract, skin, liver, breast, and adrenal glands.

Keywords: Lung; metastases; metastasis

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Introduction

Pulmonary metastases are a common occurrence in patients with extrathoracic cancer. Our goal in this chapter is to explore the complex processes of metastasis and why there is a predisposition for this to occur in the lung. In addition, we aim to describe the incidence of pulmonary metastases in various contexts and based on the origin of the primary tumor.

Pathophysiology

The process of metastatic spread involves many complex events. The pathophysiology of pulmonary metastasis

is initiated with the growth, neovascularization, and tissue invasion of the primary tumor. Subsequently, there is detachment of cells from the primary tumor and hematogenous dissemination where these cells may arrest and proliferate in capillary beds. After surviving host defense mechanisms, the tumor cells extravasate into larger arteries and extend into organs by adhering to the basement membrane (1). There are many host-factors that must act in concert for this process to occur, including cell adhesion molecules, motility, growth and angiogenesis factors and various cytokines (2,3).

There are unique characteristics of the pulmonary system that make metastases more likely to occur in the lung than anywhere else in the body. Schueller *et al.* describe these

features well, “The lungs receive the entire cardiac output every minute. They also have the densest capillary bed in the body and are the first capillary plexus that most of the lymphatic drainage meets after entering the venous system. In addition, the lungs consist of a meshwork of delicate membranes that easily entrap tumor cells which can readily draw on nearby oxygenated air for sustenance.” (4). These characteristics provide an ideal situation and environment for the cascade of events to occur that lead to metastases in the lung. The rate of growth of metastases was studied by Spratt *et al.* They performed a radiographic study of 118 patients with untreated pulmonary metastases and demonstrated, through mathematical calculation and radiographic correlation, that the rate of growth of the pulmonary metastases was exponential (5).

There are multiple routes of metastasis to the lung from extra thoracic tumors. Certain groups of extrathoracic tumors have characteristic patterns of spread attributed to the unique and complex series of events that must occur for metastasis to succeed. The most common route of metastasis is a hematogenous mechanism. This pattern of spread is first initiated with detachment of cells from the primary tumor and hematogenous dissemination of the cells into pulmonary capillary beds. A minority of these cells will survive host defense mechanisms and penetrate the pulmonary interstitium, leading to metastatic growth (6). It is also possible for the pulmonary vasculature to be seeded at the same time as dissemination in other capillary beds such as the liver, bone or brain. In addition, there are situations where hematogenous spread occurs only after other capillary beds have been seeded, such as prostate or breast cancer. Metastatic spread can also occur via lymphatic channels—regional lymph nodes become the site of collection, which commonly occurs with endobronchial metastases (7).

As previously described, pulmonary metastasis is a complex process of tumor cell dissemination from the primary tumor to the lungs. There are currently two major concepts of metastasis that may influence the approach of clinicians (8). Fidler *et al.* describes a theory of late dissemination of metastases. This is postulated to occur after genetic changes to the primary tumor and surrounding environment have occurred that are sufficient for migration and spread (9). A different theory suggests metastasis occurs via early dissemination. Morgan *et al.* describes a process of early shedding of single cancer cells. There is a subsequent dormant stage where the cells may acquire genetic and environmental alterations that trigger proper metastasis and

lead to delayed recurrence (10). Both theories of metastasis may occur separately or together within different tumor types and individuals—rendering the genetic composition and characteristics of pulmonary metastases unique and complex to treat.

For lung metastases to grow, adequate nutrition is needed via a viable blood supply. In the lung, there are three possible routes: bronchial circulation, pulmonary circulation, or both. The route of blood supply to the metastases is important as it can be a means of therapeutic intervention. Historically, it was held that most lung tumors are supplied by bronchial circulation and that pulmonary “neovascularization” did not occur (11-13). However, Milne *et al.* conducted a computer topographic angiography study of resected human lungs with pulmonary metastases of varying origin which demonstrated that angiogenesis does occur. In addition, there was a pulmonary circulation component in all metastases usually supplying the lateral portion of the tumor (14). The vascularization of pulmonary metastases is variable and complex, often recruiting supply from bronchial and pulmonary origin.

Interestingly, diet may also have a role in tumor growth. Hayman *et al.* details a study that has shown how a diet high in omega-6 fatty acids has been linked to statistically higher rates of visible lung metastases in mice injected with human breast cancer cells. As well, omega-3 fatty acids have been shown to reduce lung metastases in colorectal cancer, breast carcinoma, and melanoma (15). This is postulated to be due to influences on gene expression which can affect the production of various protein factors.

There are many biochemical factors in the tumor microenvironment that play a key role in the development of lung metastases. Laboratory studies have shown that cellular factors such as vascular endothelial growth factor (VEGF), interleukin-8 (IL-8), platelet-derived endothelial cell growth factor (PD-ECGF), and/or basic fibroblast growth factor (bFGF) play an important role in the tumor microenvironment (16). As well, tumor cells have a role in metastatic invasion with very late antigen 4 (VLA-4) production from hematopoietic progenitor cells. This production of VLA-4 allows for interaction with fibronectin in fibroblasts at premetastatic sites (17). Chemokines are activated by tumor cells through the attraction of immune cells and tumor cells to the lungs via VEGF-A, tumor necrosis factor- α (TNF- α), and transforming growth factor- β (TGF- β) inducing expression of inflammatory chemokines used for lung invasion (18). Once tumor cells are at the site of metastasis, they can anchor to the environment through

Table 1 Incidence and cumulative incidence of pulmonary metastases^o in various non-pulmonary cancer type

Tumor type	Incidence at diagnosis (%) [*]	Cumulative Incidence (%) ^{**}	Frequency of metastases restricted to the lungs (%) ^{***}
Osteosarcoma	NA	38–95	NA
Soft tissue sarcoma		66	
Renal cell carcinoma		55–75	
Testicular cancer	20–30	40–50	<5
Head and neck cancer	NA	12–41	NA
Colorectal cancer		14	2–4
Pancreatic cancer		40	0
Hepatocellular cancer		37–70	NA
Uterine cancer		5	1
Cervical cancer		10–20	25
Ovarian cancer		28	0
Breast		5	10–15
Melanoma	48	70	10
Thyroid cancer	NA	10–25	NA
Adrenocortical cancer		71	
Choriocarcinoma	60	NA	
Prostate	<1	25	0
Overall	20	20–50	NA

^o, pulmonary parenchymal metastases; ^{*}, expressed as percentage of patients presenting with the specific tumor type; ^{**}, expressed as percentage of patients with the specific tumor type; ^{***}, expressed as percentage of patients with metastases restricted to the lung (without metastases elsewhere).

surface expression of intercellular adhesion molecule 1 (ICAM-1) induced by recruited neutrophils (19). Cellular expression of proteins that enhance anchoring, recruitment of cells and invasion are necessary for lung metastasis.

Epidemiology

The lung is the most common site for cancer metastases. In addition, that most common malignant tumors found in the lung are metastases from extrathoracic tumors (4,20). Studies vary widely in reported rates of pulmonary metastases due to differences in clinical study design such as tumor type, the time period from primary tumor to pulmonary metastases, and the type and frequency of imaging used to detect them. This time period can be significant as it has been shown that pulmonary metastases have been described up to 15 years after primary cancer

detection (6). It is commonly accepted that up to half of autopsies performed on patients who died of malignancy have pulmonary metastases (21,22). Regardless of the high amount of reported lung metastases in patients with cancer, only 15% to 20% develop clinical symptoms such as cough or nonspecific chest pain from metastases (15). Van Meerbeeck *et al.* combined data from multiple autopsy series to describe the cumulative incidence of pulmonary metastases for non-pulmonary types of cancer (Table 1) (23). This shows a high incidence in urogenital and intestinal origin likely due to the cancer distribution of the population. Detterbeck *et al.* conducted a surgical series of 6,732 patients describing the incidence of primary cancer types with resected pulmonary metastases (Table 2) (24). These resected metastases were presumed “solitary” or “unique” by available staging techniques and reflect a more clinically meaningful distribution of identified

Table 2 Distribution of primary cancer types in patients with resected pulmonary metastases in a surgical series of 6,732 patients

Primary cancer type	Distribution (%)
Sarcoma	36
Teratoma	3–37
Head and neck cancer	5–24
Colon cancer	10
Breast cancer	9
Genito-urinary cancer	9
Melanoma	4
Gynecological cancer	4

pulmonary metastases. The most common sites were thyroid, colon, breast, genitourinary tract, skin, liver, breast, and adrenal glands. However, this study was biased due to “resectability”—pulmonary metastases from colon cancer may be resectable whereas systemic spread of prostate cancer is usually unresectable and therefore not reflected in this study. In summary, there are multiple ways to describe the incidence of pulmonary metastases, which varies due to clinical definition and the population studied.

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